REMARKS/ARGUMENTS

I. Support for Claim Amendments

Applicants thank the Examiner for the thoughtful comments and suggestions in the January 10, 2006 Office Action. As shown above, Applicants have amended claim 1 to recite an additional step of *comparing* TBR1 nucleotide or polypeptide levels (as reflected by the levels of agents which specifically associated with these molecules) to control levels prior to making a determination based on those levels. Support for this amendment can be found in the specification at, *e.g.*, paragraphs 202-203:

> Diagnosis involves determining the level of a polypeptide or polynucleotide of the invention in a patient and then *comparing* the level to a baseline or range. *Typically, the baseline value is representative of a polypeptide or polynucleotide of the invention in a healthy person not suffering from a mood disorder or psychosis* or under the effects of medication or other drugs. Variation of levels of a polypeptide or polynucleotide of the invention from the baseline range indicates that the patient has a mood disorder or psychosis or at risk of developing at least some aspects of a mood disorder or psychosis.

(emphasis added); see, also, paragraph 204 ("This example *compared* the mRNA levels of ... TBR1 in ... patients suffering from bipolar disorder with those found in non-psychiatric *control subjects*") (emphasis added); paragraph 215 ("The mRNA levels in all 6 layers appeared higher in the brains of bipolar patients"); paragraph 60 ("Figure 6 shows TBR1 mRNA levels in 6 layers of dorsolateral prefrontal cortex (DLPFC) in the brains of patients with bipolar disorder and *normal control subjects*").

Applicants have also amended claim 1 to recite the testing of isolated *brain tissue.* Support for this amendment can be found in the specification at, *e.g.*, paragraphs 4, 5, 25, 60 and 217. Finally, claim 1 has been amended to recite a step of associating a reagent to a "polynucleotide encoded by a nucleic acid with 95% identity to SEQ ID NO:1 or 3." Support for this amendment is found in the specification, *e.g.*, in the Examples at paragraph 208, describing

the use of TBR1 riboprobes for detecting TBR1 transcription, and the specification at paragraph 18 which defines TBR-1 (encoding by SEQ ID NO: 3) as a nucleic acid that has "greater than about 95%, preferably greater than about 96%, 97%, 98%, 99%, or higher nucleotide sequence identity, preferably over a region of at least about 25, 50, 100, 200, 500, 1000, or more nucleotides, to SEQ ID NO:1, 3, or 5 or its complement." Thus, the amendment to claim 1 does not add new matter.

Applicants have amended claim 9 to correct claim dependency.

Applicants have also added new claim 51, a dependent claim reciting the sampling of tissue from a *deceased* subject. Support for this new claim may be found in the specification at, *e.g.*, paragraphs 204-205. Thus, this claim does not add new matter.

Finally, Applicants have canceled claims 2, 4-7 and 12-50 without prejudice. Applicants reserve the right to pursue claims with scope equivalent to any of canceled claims 2, 4-7 and 12-50 in the future.

II. Rejection of Claims 1, 3-4, 6, 7-9 and 11 under 35 U.S.C. § 112, paragraph 1

The Examiner rejected claims 1, 3-4, 6, 7-9 and 11 under 35 U.S.C. § 112, paragraph 1 as non-enabled. See Office Action at page 3. After describing Applicants' disclosure and the prior art, the Examiner concluded that, "the art indicates the invention will not work under most circumstances" and also that, "there is no guidance in the specification as to how to measure [changes in TBR1 mRNA levels] other than in postmortem patients already having been diagnosed with bipolar illness." See Office Action at pages 5 and 6, respectively. The Examiner also argues on page 6 of the Office Action that Applicants' claims are not enabled because "there is no guidance in the specification as to how to measure [TBR1 mRNA levels] other than in postmortem patients already having been diagnosed with bipolar illness."

Applicants respectfully disagree with the Examiner.[1] Applicants' specification enables the pending claims because (1) postmortem brain expression patterns relate reasonably well to

[1] As an initial matter, Applicants note that the Examiner's arguments are largely mooted by Applicants' claim amendments. To the extent the Examiner's arguments are rendered moot, Applicants do not address them nor do

expression patterns in living brains; and (2) the techniques required to practice Applicants' invention do not require undue experimentation on the part of those skilled in the art (on the contrary, the techniques are standard).

The enablement standard of 35 U.S.C. § 112 does not require Applicants to teach the skilled practitioner what the skilled practitioner already knows. A patent need not teach, and preferably omits, what is well known in the art. *See* MPEP 2164.01 (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Likewise, it is not necessary for Applicants' to specify every sub-step in the method(s) of practicing the invention if it is known to one skilled in the art that such information could be obtained without undue experimentation. *See* MPEP 2164.01(c); *see also* MPEP 2164.02 (citing *In re Borkowski*, 422 F.2d 904, 908 (CCPA 1970)). With all due respect to the Examiner's analysis under *Wands*, the detection of mRNA expression levels in the human brain does not require undue experimentation nor are the techniques involved especially "complex," as Applicants show in more detail below.

A. Post-mortem brain studies are recognized by those of skill in the art as appropriate models for determining *in vivo* expression patterns.

Skilled artisans have long been aware that the study of post-mortem human brains was relevant to understanding the biology of the living subjects from whom the brains were isolated. This is why post-mortem studies have been and continue to be a recognized source of useful information for scientists and physicians. Applicants have attached to this Response publications showing the solid and predictable relationship between post-mortem and living brain tissue. For example, the Franz *et al.* reference shows that researchers' well-considered reliance on post-mortem brains was entirely justified:

> We found that despite the large impact that death as such and, potentially, surgery have on gene expression patterns in autopsy and resection samples, respectively, *differences between brain regions that exist in the living brain are mostly retained in postmortem samples*.

Applicants admit the accuracy of the Examiner's descriptions of the art and Applicants' claims. Applicants do seek to place the claims in condition for allowance, however, without unnecessary delay. Achieving this goal is the primary reason for the above-mentioned claim amendments.

See Franz *et al.*, page 6, bottom of first column (emphasis added). Although Franz *et al.* found that a small portion of genes (roughly 10%) are consistently differentially expressed in living versus post-mortem brains, Franz *et al.* note that the differentially expressed genes are mostly:

> [g]enes involved in rather basic functions, such as RNA processing, protein biosynthesis and transport, organelle organization and biogenesis, the ubiquitin cycle, and DNA repair (Table 1) are over-represented among genes differently expressed between autopsies and resections.

See Franz *et al.*, page 6, middle of column 2. Applicants' claims do not involve the detection of the sort of "housekeeping" genes described by Franz *et al.* Rather, Applicants' claims are drawn to methods of detecting the expression of mRNA encoding TBR1, a transcription factor expressed in cells of the vertebrate central nervous system. See, *e.g.*, specification at paragraph 64. Thus, Franz *et al.* simply provide another confirmation of what neurologists have reasonably believed to be true for many years: studying post-mortem brains is a reliable method of obtaining information about living brains.

Applicants also provide a review published in the *Journal of Chemical Neuroanatomy* (Bahn *et al.*, "Gene expression profiling in the post-mortem human brain -- no cause for dismay," (2001) 22: 79-94) showing that skilled artisans have known for some time how to obtain post-mortem brain samples that accurately reflected the *in vivo* state of the subjects from whom the samples were taken. The Bahn *et al.* abstract teaches that "post-mortem tissue undoubtedly is the fundamental prerequisite to investigate complex brain disorders with molecular profiling techniques." In the body of the publication, Bahn *et al.* teach further:

> [W]ith appropriate tissue preparation the structural integrity of post-mortem tissue can be preserved allowing for detailed morphological, morphometrical, and ultrastructural investigations e.g. (Benes, 1988); Ravid et al., 1992; Vonstattel et al., 1995; Waldvogel et al., 1999). . . . Furthermore, high throughput mRNA expression profiling is possible using post-mortem human brain tissue and data from our laboratories demonstrate that robust and reproducible results can be achieved . . . . *Post-mortem human brain material is a precious and valuable resource for molecular studies.*

See Bahn *et al.*, pages 79-80 (emphasis added).[2]

The Federal Circuit has held that Applicants are required to show that the art recognizes a *reasonable* correlation between a model (e.g., post-mortem brains) and the claimed method, not a "rigorous" or "invariable" correlation. *See Cross v. Itzuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985); *see also* MPEP 2164.02. Applicants have provided evidence which satisfies this requirement. Applicants respectfully submit that the Examiner has not provided any evidence clearly showing that Applicants' (or any neurologists') reliance on expression patterns in post-mortem brains is misplaced or unreasonable.

B. Measuring mRNA in isolated brain tissue does not require undue experimentation.

As discussed above, the Examiner argues on page 6 of the Office Action that Applicants' claims are not enabled because "there is no guidance in the specification as to how to measure [TBR1 mRNA levels] other than in postmortem patients already having been diagnosed with bipolar illness." Applicants respectfully submit that the measurement of mRNA in isolated tissue of the brain, whether the brain tissue is that of postmortem patients or living patients, does not require undue experimentation on the part of the skilled practitioner. Applicants describe in detail in the specification how mRNA expression levels are determined in the isolated brain tissue of post-mortem patients. *See, e.g.*, specification at pages 56-59.

Applicants recognize that isolating the tissue of living brains is not without risks. That a procedure has risks, however, does not mean that the procedure requires undue experimentation. If the opposite were true, no medical procedure could be patented. In fact, tissue biopsies of living brains are routinely taken for diagnostic purposes when a patient is believed to be suffering from a potentially deadly neurological illness.[3] Alternatively, when a patient has

[2] The complete citations for the references in the quoted passage from Bahn *et al.* follow: Benes F.M. (1988) *Psychiatr. Dev.*, 6:213–226; Ravid R. *et al.* (1992) *Prog. Brain. Res.*, 93:83–95; Vonsattel J.P. *et al.* (1995) *J. Neuropathol. Exp. Neurol.*, 54:42–56; Waldvogel H.J. *et al.* (1999) *J. Comp. Neurol.*, 415:313–340.

[3] Applicants note that the U.S. Patent Office routinely issues patents reciting claims drawn to brain biopsies without limiting such claims to post-mortem biopsies, *e.g.*, U.S. Pat. No. 6,834,237, issued Dec. 21, 2004 (priority date: June 1, 2001); U.S. Pat. No. 6,794,138, issued (priority date: Sept. 24, 2001); U.S. Pat. No. 6,756,586, issued June 29, 2004 (priority date: June 21, 2002).

experienced brain trauma (*e.g.*, from a self-inflicted fall) and is suspected of suffering from a disorder of the brain such as bipolar disorder, a brain biopsy could be obtained during the course of life-saving surgery. Measuring mRNA in tissue taken from a living patient does not require the use of any techniques beyond the well-known techniques needed to measure mRNA in tissue obtained from deceased patients (discussed above).

For all of the forgoing reasons, Applicants claims meet the enablement requirement of 35 U.S.C. § 112. Withdrawal of the Examiner's rejections and allowance of the claims are earnestly solicited.

III. Rejection of Claims 1, 3-4, 6, 7-9 and 11 under 35 U.S.C. § 112, paragraph 2

The Examiner rejected claims 1, 3-4, 6, 7-9 and 11 under 35 U.S.C. § 112, paragraph 2, "as being incomplete for omitting essential steps, such omission amounting to a gap between the steps." See Office Action at page 6. Applicants respectfully submit that their amendment to claim 1, discussed above, renders this rejection moot.

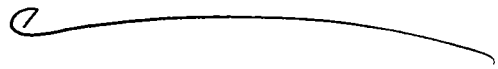
The Examiner also rejected claims 1, 3-4, 6, 7-9 and 11 under 35 U.S.C. § 112, paragraph 2, because the term "stringency" is allegedly "relative" and not "unambiguously" defined in the specification. See *id.* Again, Applicants respectfully submit that the amendment to the pending claims renders this rejection moot.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Chris J. Ullsperger
Reg. No. 48,006

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300

CJU:jc
Attachments:

1. Bahn, *et al.,* Gene expression profiling in the post-mortem human brain - no cause for dismay; Journal of Chemical Neuroanatomy 22 (2001) 79-94;

2. Franz, *et al.,* Systematic analysis of gene expression in human brains before and after death; Genome Biology 2005, 6:4112.

60741447 v1